北京大学
PEKING UNIVERSITY

北京国际数学研究中心
BEIJING INTERNATIONAL CENTER FOR MATHEMATICAL RESEARCH

2016 A3 Workshop on Interdisciplinary Research Connecting Mathematics and Biology

Peking University

April 22-24, 2016

北京大学 PEKING UNIVERSITY

北京国际数学研究中心 BEIJING INTERNATIONAL CENTER FOR MATHEMATICAL RESEARCH

2016 A3 Workshop on Interdisciplinary Research Connecting Mathematics and Biology

Dates: April 21: Registration; April 22 – 24: Workshop

Venue: Lecture Hall, JingChunYuan No. 82 JiaYiBing, BICMR, Peking University

Scientific committee:

Pingwen Zhang (Peking University)

Qing Nie (Peking University & UC Irvine)

Yuan Lou (Ohio State & RenMin University)

Yasumasa Nishiura (Tohoku University)

Eun Ok Jung (Konkuk University)

Hyeonbae Kang (Inha University)

Organizing committee:

Lei Zhang (Peking University, China)

Wei Lin (Fudan University, China)

Gouhei Tanaka (University of Tokyo, Japan)

Jae Kyoung Kim (KAIST, Korea)

Sponsors:

NSFC Tianyuan Foundation
NSFC Key Project for A3 Foresight Program
Key Lab of Mathematics and Applied Mathematics (PKU), Ministry of Education
Beijing International Center for Mathematical Research (BICMR)
PKU Interdisciplinary Research Laboratory of Mathematics and Biology (Bio-Math Lab)

Accommodation:

Hotel address: "Zhong Guan Xin Yuan" Hotel (Zhongguanyuan Global Village)
No. 216 Zhongguancun North Road, Haidian District, Beijing 100871, China
Hotel website: www.pkugv.com
Hotel Tel.: + (86 10) 62752288

Workshop webpage:

http://bicmr.pku.edu.cn/content/show/17-1666.html

Contact: Tian Tian, email: ttian@math.pku.edu.cn

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Workshop Program

Day 1 (April 22, 2016)

Morning Session Chair: Lei Zhang		
Time	**People**	**Titles /Activities**
8:20-8:30	**Opening remarks**	
8:30-9:15	Jianfeng Feng (Fudan)	Big Data and Brain Science: Stepping into Patients Mind
9:20-9:50	Ah-Ram Kim (Handong Univ)	Systems biology analysis of altered gene expression in human and a model organism Drosophila
9:50-10:20	**Coffee Break**	
Chair: Ah-Ram Kim		
10:20-10:50	Tiejun Li (PKU)	Energy Landscape and the two-scale large deviations for biological stochastic dynamics
10:55-11:25	Eun Bo Shim (Kangwon National U.)	Image-based simulation model of flow reserve in heart and brain vascular system
11:30-12:00	Gouhei Tanaka (U. of Tokyo)	Bifurcation analysis for cellular dynamics
12:00-14:00	**Lunch**	
Afternoon Session Chair: Gen Kurosawa		
14:00-14:30	Eun Ok Jung (Konkuk U.)	A heart model in the whole circulatory system
14:35-15:05	Dan Hu (SJTU)	Optimization, Adaptation, and Initiation of Biological Transport Networks
15:10-15:40	Chang Hyeong Lee (UNIST)	Reaction Systems and Applications
15:40-16:10	**Coffee Break**	
Chair: Gouhei Tanaka		
16:10-16:40	Gen Kurosawa (Riken)	Temperature and biological timing
16:45-17:15	Jae Kyoung Kim (KAIST)	The mechansims for robust circadian timekeeping
18:00	**Dinner**	

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Day 2 (April 23, 2016)

Morning Session **Chair: Yuan Lou**		
Time	**People**	**Titles /Activities**
8:30-9:15	Mariko Okada (Riken)	Experimental and modeling analysis of signal transduction network in mammalian cells
9:20-9:50	Qing Nie (PKU & UCI)	Cell Plasticity and Multi-step Transition in Development and Cancer
9:50-10:20	**Coffee Break & Group Photo**	
Chair: Yasumasa Nishiura		
10:20-10:50	Shinji Nakaoka (U. of Tokyo)	Investigation for population kinetics of reservoir cells in HIV infection
10:55-11:25	Luonan Chen (CAS)	From phase-transition to distribution-transition with strong noise, detected by dynamical network markers
11:30-12:00	Jinzhi Lei (Tsinghua)	The dual roles of autophagy in cancer development
12:00-14:00	**Lunch**	
Afternoon Session **Chair: Wei Lin**		
14:00-14:45	Kwang-hyun Cho (KAIST)	Systems Biology: From Circuit Dynamics Toward Network Control
14:50-15:20	Hao Ge (PKU)	Nonequilibrium stochastic dynamics at single cell level
15:20-15:50	**Coffee Break**	
Chair: Jae Kyoung Kim		
15:50-16:20	Koichi Saeki (SOKENDAI)	Optimal T cell cross-reactivity and the role of regulatory T cells
16:25-16:55	Yangjin Kim (Konkuk U.)	The role of the microenvironment in regulation of cell infiltration in glioblastoma
17:00-17:30	Wei Lin (Fudan U.)	TBD
18:00	**Dinner**	

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Day 3 (April 24, 2016)

9:00-12:00	**Free discussion**

Abstract

1. **Big Data and Brain Science: Stepping into Patients Mind**
   Jianfeng Feng
   Fudan University & Warwick University
   Abstract:

2. **Systems biology analysis of altered gene expression in human and a model organism Drosophila**
   Ah-Ram Kim
   Handong University
   Abstract: A major objective of high throughput genomics has been to understand genetic mechanisms underlying complex traits of human disease. Recent genome-wide association studies (GWAS) and in vivo analysis of DNase I hypersensitive binding sites in the genome have shown that the majority of disease-associated variants are concentrated in regulatory DNA. Systematic comparisons of expression quantitative trait loci (eQTL) and GWAS suggest that many intergenic variants associated with complex phenotypes result in alteration of gene expression. Therefore, investigating the transcriptional effects of disease-associated genetic variants among individuals will be essential for a fundamental understanding of the genetic basis of human disease. In order to understand how genetic variations result in distinctive transcriptional behaviors, the causal variants and their influence on transcriptional regulation must be elucidated. One of main limitations of current statistical approaches is that it is very difficult to identify and validate the causal variants. Furthermore, because gene expression is orchestrated by simultaneously operating molecular interactions on the regulatory DNA, it is not currently tractable to determine the full effects of such complex interactions by contemporary experimental and statistical approaches alone. In this talk, I will introduce recent advances in computational modeling of transcriptional regulation to systematically explore the relationship between regulatory DNA and altered altered gene gene expression.

3. **Energy Landscape and the two-scale large deviations for biological stochastic dynamics**
   Tiejun Li
   Peking University
   Abstract: The construction of energy landscape for bio-dynamics is attracting more and more attention recent years. In this talk, I will introduce the strategy to construct the landscape from the connection to rare events, which relies on the large deviation theory for Gillespie-type jump dynamics. In the application to a typical genetic switching model, the two-scale large deviation theory is developed to take into account the fast switching of DNA states. The comparison

with other proposals are also discussed. We demonstrate different diffusive limits arise when considering different regimes for genetic translation and switching processes. This is a joint work with Fangting Li, Xianggang Li and Cheng Lv.

4. **Image-based simulation model of flow reserve in heart and brain vascular system**
Eun Bo Shim
Kangwon National University
Abstract: Flow reserve is a critical physiological index indicating the capability of a conduit blood vessel whether it can transport enough blood to tissue even in the microvascular hyperemic condition. Conventional method to obtain this index is invasive measurement coupled with drug induced hyperemia. However, this method may cause side effects to patients due to invasive measurement and there are many patients who do not respond to the drug because of too fast metabolism. Recently, it was shown that simulation approach based on computational method and physiological modeling of vascular system can be an alternative to calculate the index. Since this approach is non-invasive and drug effect is mimicked by virtual model, this became an effective method in determining coronary flow reserve. However, there are several questions related to the physiological accuracy and efficacy of the method because it is a complicated approach coupling arterial vascular hemodynamics to microvascular and venous physiological properties. In this presentation, we introduce the physiological basics of the approach in heart and brain and then present our simulation results of clinical applications in coronary and neurovascular system. Also limitations and future direction of the approach are discussed.

5. **Bifurcation analysis for cellular dynamics**
Gouhei Tanaka
The University of Tokyo
Abstract: Bifurcation analysis is a powerful tool for specification of qualitative changes in nonlinear dynamics of cellular systems. In this talk, we show a bifurcation analysis of a mathematical model for NF-kappaB signaling pathway. The transcription factor NF-kappaB plays a significant role in regulating the immune response to infection and associated with auto-immune diseases, cancers, and other disorders. In order to clarify the relationship between the behavior of NF-kappaB and its functionality, it is vital to understand how NF-kappaB responds to various stimuli. The signal transduction pathways associated with NF-kappaB have been intensively studied in both experiments and model simulations, but the mechanism behind the regulation of NF-kappaB is still not fully uncovered. Our analysis is focused on oscillatory behavior and switch-like responses, both of which are considered to be important for

downstream gene expressions. We reveal the mechanism of the onset of oscillatory behavior and the emergence of the switch-like response. This is the collaborative work with K. Inoue, M. Okada, and K. Aihara.

6. **A heart model in the whole circulatory system**
   Eun Ok Jung
   Konkuk University
   Abstract: We present simulations of left and right PDE heart model governed by the partial differential equations. This heart model is coupled with a lumped model of the whole circulatory system governed by the ordinary differential equations. The immersed boundary method is used to investigate the intracardiac blood flow and the cardiac valve motions of the normal circulation in normal human case. We investigate the intraventricular velocity field and the velocity curves over the mitral ring and across outflow tract. The pressure and flow are also measured in the left and right heart and the systemic and pulmonary arteries. The simulation results are comparable to the existing measurements. We extend this multi-dimensional circulatory model to the ventricular septal defect (VSD) disease. A VSD is a defect (hole) in the ventricular septum, the wall dividing the left and right ventricles of the heart. We investigate how this defect (hole) size affects the flow in the pulmonary circulatory part.

7. **Optimization, Adaptation, and Initiation of Biological Transport Networks**
   Dan Hu
   Shanghai JiaoTong University
   Abstract: Blood vessel systems and leaf venations are typical biological transport networks. The energy consumption for such a system to perform its biological functions is determined by the network structure. In the first part of this talk, I will discuss the optimized structure of vessel networks, and show how the blood vessel system adapts itself to an optimized structure. Mathematical models are used to predict pruning vessels in the experiments of zebra fish. In the second part, I will discuss our recent modeling work on the initiation process of transport networks. Simulation results are used to illustrate how a tree-like structure is obtained from a continuum adaptation equation system, and how loops can exist in our model. Possible further application of this model will also be discussed.

8. **Reaction Systems and Applications**
   Chang Hyeong Lee
   Ulsan National Institute of Science and Technology
   Abstract: A reaction system is the system in which various reactions occur between several physical, chemical or biological species. In this talk, we present stochastic models and computational methods for describing the reaction system and show some results obtained by applying the methods to motivating


examples including biochemical systems and epidemic models.

9. **Temperature and biological timing**
Gen Kurosawa
Theoretical Biology Laboratory, RIKEN
Abstract: Most biological phenomena are sensitive to temperature change. For example, biochemical reaction and cell growth accelerate with temperature. In contrast, the period (~24h) of our circadian rhythm is relatively insensitive to temperature. This property, so-called "temperature compensation" can be applied not only to poikilotherms but also to homoiotherms. In this study, we considered theoretically and experimentally the mechanism of temperature compensation. Experiments have shown that periodic gene activities underlie circadian rhythms at behavioral level such as sleep-wake cycles, and regulatory networks of genes and proteins generate the periodic gene activities. To understand the mechanism of temperature compensation, we numerically and mathematically analyzed the conditions of robust period for multiple models with different network topologies. Unexpectedly, we found that geometric mean amplitude should increase along with increasing temperature and reaction speed to stabilize the period for all the models we studied. To validate temperature-sensitive amplitude(s) for robust period, which we call "temperature-amplitude coupling", we measured the time-series of circadian gene activities in mammalian cultured cells. We confirmed that the amplitude(s) of gene activities tend to increase at higher temperature. This is the collaborative study with Drs. Atsuko Fujioka, Satoshi Koinuma, Atsushi Mochizuki, and Yasufumi Shigeyoshi.

10. **The mechansims for robust circadian timekeeping**
Jae Kyoung Kim
Korea Advanced Institute of Science and Technology
Abstract: The circadian clock in the hypothalamus functions as an accurate timekeeper of physiological events by maintaining 24-hr periodic rhythms even in the presence of intrinsic and extrinsic perturbations. While many genes and proteins underlying the circadian clock have been identified, how they work together to generate robust rhythms remains unclear. This problem was selected as one of 125 important science puzzles for the present century by Science magazine. In this talk, I will discuss how mathematical modeling combined with experiments can reveal key molecular mechanisms that underlie robust rhythmicity in the face of perturbations, such as temperature change and external signals.

11. Experimental and modeling analysis of signal transduction network in mammalian cells

Mariko Okada-Hatakeyama
RIKEN Center for Integrative Medical Sciences

Abstract: Intracellular signaling pathways are important to determine the activation of transcription factors, and their dynamics is often associated with determination of particular cellular phenotypes. Interestingly, signaling pathways often control these processes in a nonlinear fashion. In this talk, digital activation mechanisms of NF-kappaB transcription factor, which plays an important role in cellular commitment and disease progression, will be described. Based on wet-lab experiments and mathematical modeling, we showed that NF-κB activity is controlled by several feedback loops within the signaling pathway to show switch-like activation and oscillation dynamics These feedback loops contribute to determine the threshold for NF-kappaB-mediated gene expression, suggesting that the regulatory mechanism is important for B cell lineage commitment.

12. Cell Plasticity and Multi-step Transition in Development and Cancer

Qing Nie
Peking University and U. of California, Irvine

Abstract: Reversible epithelial-to-mesenchymal transition (EMT) is central to tissue development, epithelial stemness, and cancer metastasis. While many regulatory elements have been identified to induce EMT, the complex process underlying such cellular plasticity remains poorly understood. Utilizing a systems biology approach integrating modeling and experiments, we found multiple intermediate states contributing to EMT and that the robustness of the transitions is modulated by transcriptional factor Ovol2. In particular, we obtained evidence for a mutual inhibition relationship between Ovol2 and EMT inducer Zeb1, and observed that adding this regulation generates a novel four-state system consisting of two distinct intermediate phenotypes that differ in differentiation propensities and are favored in different environmental conditions. We identified epithelial cells that naturally exist in an intermediate state with bidirectional differentiation potential, and found the balance between EMT-promoting and -inhibiting factors to be critical in achieving and selecting between intermediate states. Our analysis suggests a new design principle in controlling cellular plasticity through multiple intermediate cell fates and underscores the critical involvement of Ovol2 and its associated molecular regulations.

13. Investigation for population kinetics of reservoir cells in HIV infection

Shinji Nakaoka
The University of Tokyo

Abstract: HIV infection is a worldwide spreading infectious disease. A standard protocol of HIV treatment, referred to as anti-retroviral therapy (ART), consists of simultaneous injection of multiple different types of drug including resverse-transcriptase, protease, and entry inhibitors. Despite of extensive efforts on the eradication program of HIV, complete elimination of HIV in a host-body has been failing. One important mechanism underlying HIV persistence in a host-body is the existence of reservoir cells which harbor HIV during their resting period.

Suspected cell types that harbor HIV include resting memory CD4 positive T cells which normally live in lymphoid tissues (LTs). Several clinical studies suggest the importance of LTs as a major environment for HIV reservoir. Main possible mechanisms causing HIV reservior include insufficient delivery of drug to LTs (Flecher et al 2012 PNAS) as LTs serve an ideal place for HIV to hide from drug and another attack (R. Lorenzo-Redondo et al. Nature 2016). Although extensive mathematical studies have ever been conducted on HIV infection dynamics, less incorporate structure and function of LTs in infection dynamics explicitly.

In the preceding our study (Nakaoka, Iwami and Sato 2015, J. Math. Biol.), we constructed a mathematical model describing HIV infection in LT network. Effect of cell migration across the LTs and blood on HIV persistence are quantitatively investigated by employing the basic reproduction number. Here we present recent progresses on modeling HIV infection dynamics to incorporate heterogeneity in LTs and mutant variation of HIV, both of which are implicated as major promotive factors of HIV persistence.

14. From phase-transition to distribution-transition with strong noise, detected by dynamical network markers

Luonan Chen
Chinese Academy of Sciences

Abstract: Identifying early-warning signals of a critical transition for a complex system is difficult, especially when the target system is constantly perturbed by big noise, which makes the traditional methods fail due to the strong fluctuations of the observed data. In this work, we show that the critical transition is not traditional state-transition but probability distribution-transition when the noise is not sufficiently small, which, however, is a ubiquitous case in real systems. We present a model-free computational method to detect the warning signals before such transitions. The key idea behind is a strategy: “making big noise smaller” by a distribution-embedding scheme, which transforms the data from the observed state-variables with big noise to their distribution-variables with small noise, and thus makes the traditional criteria effective because of the

significantly reduced fluctuations. Specifically, increasing the dimension of the observed data by moment expansion that changes the system from state-dynamics to probability distribution-dynamics, we derive new data in a higher dimensional space but with much smaller noise. Then, we develop a criterion based on the dynamical network marker (DNM) to signal the impending critical transition using the transformed higher dimensional data. We also demonstrate the effectiveness of our method in biological, ecological and financial systems.

15. The dual roles of autophagy in cancer development

Jinzhi Lei
Tsinghua University

Abstract: Autophagy is a survival pathway for tumor cells in preventing the accumulation of damaged proteins in organelles in tissues. There has been great interest in inhibiting autophagy for cancer therapy. Nevertheless, the effect of autophagy inhibition is often context dependence in pancreatic cancer due to the dual roles of autophagy in carcinogenesis and malignant transformation. Autophagy inhibition can accelerate tumor initiation, and attenuate the late-grade tumor growth. Here, we developed a mathematical model to investigate how the competition of the dual roles of autophagy regulate pancreatic cancer development. We showed that variations in p53 expression level can change the role of autophagy in pancreatic cancer development by affecting the competition between its anti-transformation and pro-survival mechanisms.

16. Systems Biology: From Circuit Dynamics Toward Network Control

Kwang-Hyun Cho
Korea Advanced Institute of Science and Technology

Abstract: Systems biology explores the emergent property of living systems by combining biological experimentation, mathematical modeling, and computer simulation. Such an emergent property occurs when multiple components interact with each other in a nonlinear way. Cells have evolved a complicated signaling network to recognize external signals and produce appropriate responses for survival. We found that there are intriguing circuits in such a signaling network that were evolutionarily designed to elicit critical functions as an emergent property. In particular, we found that feedforward and feedback loops are essential in such circuits and that cellular dysfunctions related to complex human disease such as cancer can be caused by malfunctioning of these circuits. In this talk, I will briefly review the main concept and history of systems biology and then introduce some case studies ranging from a small-scale signaling circuit to a large and complex molecular interaction network to discuss how the emergent properties of cellular functions can be induced by complicated interaction of multiple molecules and how we can control the cellular functions by perturbing some targeted molecules in the network.

17. Nonequilibrium stochastic dynamics at single cell level

Hao Ge
Peking University

Abstract: Stochastic processes become more and more popular to model the mesoscopic nonequilibrium biophysical dynamics, which well fit the recent development of advanced experimental techniques at single-cell level.

Here I will take about two short stories. One is the molecular mechanism of transcriptional burst, which is uncovered by both single-molecule in vitro experiments and stochastic models. The other is a new rate formula for phenotype transition at the intermediate region of gene-state switching for single cells, the rigorous proof of which needs to integrate the well-known Donsker-Varadhan theory and Freidlin-Wentzell theory of large deviation principle. The new rate formula can explain a "noise enhancer" therapy for HIV reported in a Science paper last year, which motivated a future project of us.

18. Optimal T cell cross-reactivity and the role of regulatory T cells

Koichi Saeki[1], Hilje M. Doekes[2] and Rob J. De Boer[2]
[1]*Department of Evolutionary Studies of Biosystems School of Advanced Sciences, The Graduate University for Advanced Studies.*
[2]*Theoretical Biology & Bioinformatics, Department of Biology, Utrecht University*

Abstract: The T lymphocytes of the adaptive immune system constitute a very diverse repertoire of clones expressing a unique T cell receptor (TCR). It has been argued that TCRs are cross-reactive, meaning that one receptor can recognize a multitude of epitopes. Cross-reactivity between self and foreign epitopes can potentially lead to autoimmune responses. Regulatory T cells (Tregs) down-regulate immune reactions, and play an important role in the avoidance of autoimmunity. We use a probabilistic modeling approach to investigate how suppression of antigen-presenting dendritic cells (DCs) by Tregs influences the probability of mounting a successful immune response against a pathogen while remaining self-tolerant. For T cell cross-reactivity values close to experimental estimates, we find that the presence of Tregs increases this success probability somewhat. However, the probability on a successful immune response remains relatively low for these cross-reactivity values, and the probability of success is optimized when T cells are more specific and no Tregs are formed. We conclude that DC suppression on its own is insufficient to provide an evolutionary benefit of regulatory T cells. Rejecting one intuitively likely hypothesis for the function of Tregs has narrowed down the search for the mechanisms by which they are suppressing inappropriate immune responses.

19. The role of the microenvironment in regulation of cell infiltration in glioblastoma

Yangjin Kim
Konkuk University

Abstract: Malignant gliomas are the most common type of brain cancer, which arise from glial cells, and in their most aggressive form are called GBMs. GBMs are highly invasive and difficult to treat because cells migrate into surrounding healthy brain tissue rapidly, and thus these tumors are difficult to completely remove surgically. GIMs, which can comprise up to one third of the total tumor mass [1], are present in both intact glioma tissue and necrotic areas. They apparently originate from both resident brain macrophages (microglia) and newly recruited monocyte-derived macrophages from the circulation. Activated GIMs exhibit several phenotypes: one called M1 for classically activated, tumor suppressive, and another called M2 for alternatively activated, tumor promoting, and immunosuppressive [2]. Within a tumor the balance between these phenotypes is typically shifted to the M2 form [3]. Numerous factors secreted by glioma cells can influence GIM recruitment and phenotypic switching, including growth factors, chemokines, cytokines and matrix proteins [4], [5]. In this work, we focus on mutual interaction between a glioma and M1/M2 microglia mediated by CSF-1, TGFbeta, and EGF. Up-regulated TGFbeta leads to up-regulation of Smad within the tumor cells and secretion of MMPs, leading to proteolysis for EMT process and cell infiltration. The mathematical model consists of densities of glioma cells, M1 type cells, M2 type cells, and concentrations of CSF-1, EGF, TGFbeta, Extracellular matrix, and MMPs. We developed the model to investigate the mutual interactions between tumor cells in the upper chamber and microglia in the lower chamber. In the experiments, Boyden invasion assay was used to show that this mutual interaction induces glioma infiltration in vitro and in vivo. We show that our simulation results are in good agreement with the experimental data and we generate several hypotheses that should be tested in future experiments in vivo.

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epidermal growth factor receptor (EGFR) and colony stimulating factor 1 receptor (CSF-1R) signaling," Molecular medicine, vol. 18, no. 3, p. 519, 2012.
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20. **TBA**
Wei Lin, Fudan University